REACTIONS OF URACILS; 3[1]

PYRAZOLO[3,4-d]- AND PYRIDO[2,3-d]PYRIMIDINES FROM 5-FORMYL-1,3-DIMETHYLURACILS

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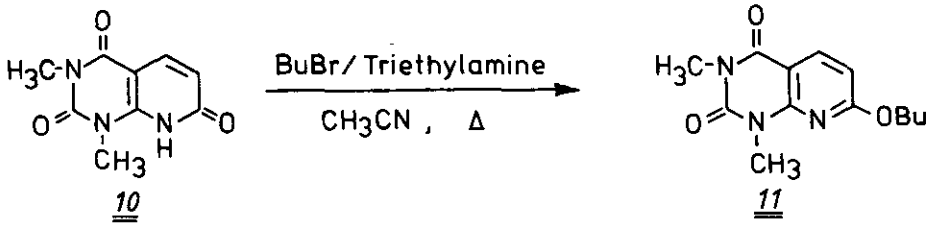
Abstract — Starting from the known 5-formyl-1,3-dimethyluracils (1a,b) some novel derivatives having a great biological interest have been synthesized. The constitutions of the products obtained were established based on spectral data.

The biological activities of pyrimidines containing acyl and/or olefinic functions at position-5 have stimulated considerable research in this field[3-5]. Continuing our work on the synthesis of uracils of potential biological activity[1], we report here some reactions of 5-formyl-1,3-dimethyluracils to new derivatives and the synthesis of several, otherwise hardly accessible new 2,4,7-trioxopyrido[2,3-d]pyrimidines. It has been reported that the recation of 1a with phenyl- or methylhydrazine yielded the Schiff's bases which upón heating gave N-substituted pyrazolo[3,4-d]-pyrimidines[6]. We have extended this reaction to (6-chloro-3-pyridazinyl)-hydrazine 2 in order to investigate the influences of the heteroaromatic ring and the adjacent ring N-atoms on the stability of the intermediate as well as on the formation of pyrazolo[3,4-d]pyrimidine derivative. Thus, 1a condensed with 2 to afford the arylidene derivative 3, which reacted smoothly with aqueous methylamine to give 4. In contrast to the behaviour of the phenyl analogue, the *intra*molecular cyclization tendency of 3 was considerably low due to the -I effect of the 3-pyridazinyl ring: only the thermal reaction at 180°C of 3 afforded 5 in moderate yield, while the cyclization was unsuccessful in ethanol in the presence of equimolar amounts of triethylamine. On the basis of spectral data the formation of the theoretically also possible tricycle 6 could be ruled out. The *E*-3-(5-uracilyl)acrylic acid derivatives 7a,b were synthesized by Wittig or Knoevenagel-Doebner reaction, respectively.

An investigation was undertaken to explore the potential utility of the reactions

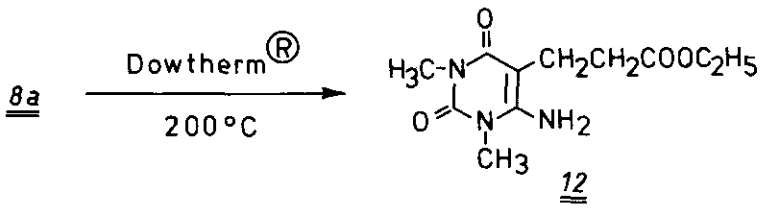
of some nucleophiles with 7a as a route for the synthesis of fused ring systems. It has been found that under kinetic control primary aliphatic amines or ammonia react with 7a to yield 8a-c. Upon heating of 8a,b in triethylamine in the presence of catalytic amount of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), the novel 2,4,7-trioxopyrido[2,3-d]pyrimidines 9a,b were obtained in high yield.

Since the alkylation of 1,3-dimethyl-2,4,7-trioxopyrido[2,3-d]pyrimidine 10[8] with butyl bromide (or iodide) leads to the formation of the 7-butoxy derivative 11, our method provides a simple and efficient approach to the synthesis of the potentially biological active 8-substituted 2,4,7-trioxopyrido[2,3-d]pyrimidines.



10 11

In contrast to the behaviour of 8a toward the triethylamine/DBN system, it reacted in Dowtherm®A at 200°C to the desalkylated derivative 12, presumably *via* two consecutive sigmatropic 1,5-H shifts:



12

The constitution of 12 was established based on spectral data. Thus, in the ^{1}H NMR spectrum the absence of an AB quartet being characteristic for the olefinic protons and the lack of the butyl protons, as well as the presence of $-(CH_2)_2-$ and NH_2 protons pointed unambigously to the constitution of 12. Moreover, also IR, MS, and ^{13}C NMR[9] data were of further evidence for this structural proposal. Now, the behaviour of several other mono- and bifunctional nucleophiles towards 7a as well as the mechanism of formation of 12 is under investigation. Work in progress together with the full preparative details will be published elsewhere[10].

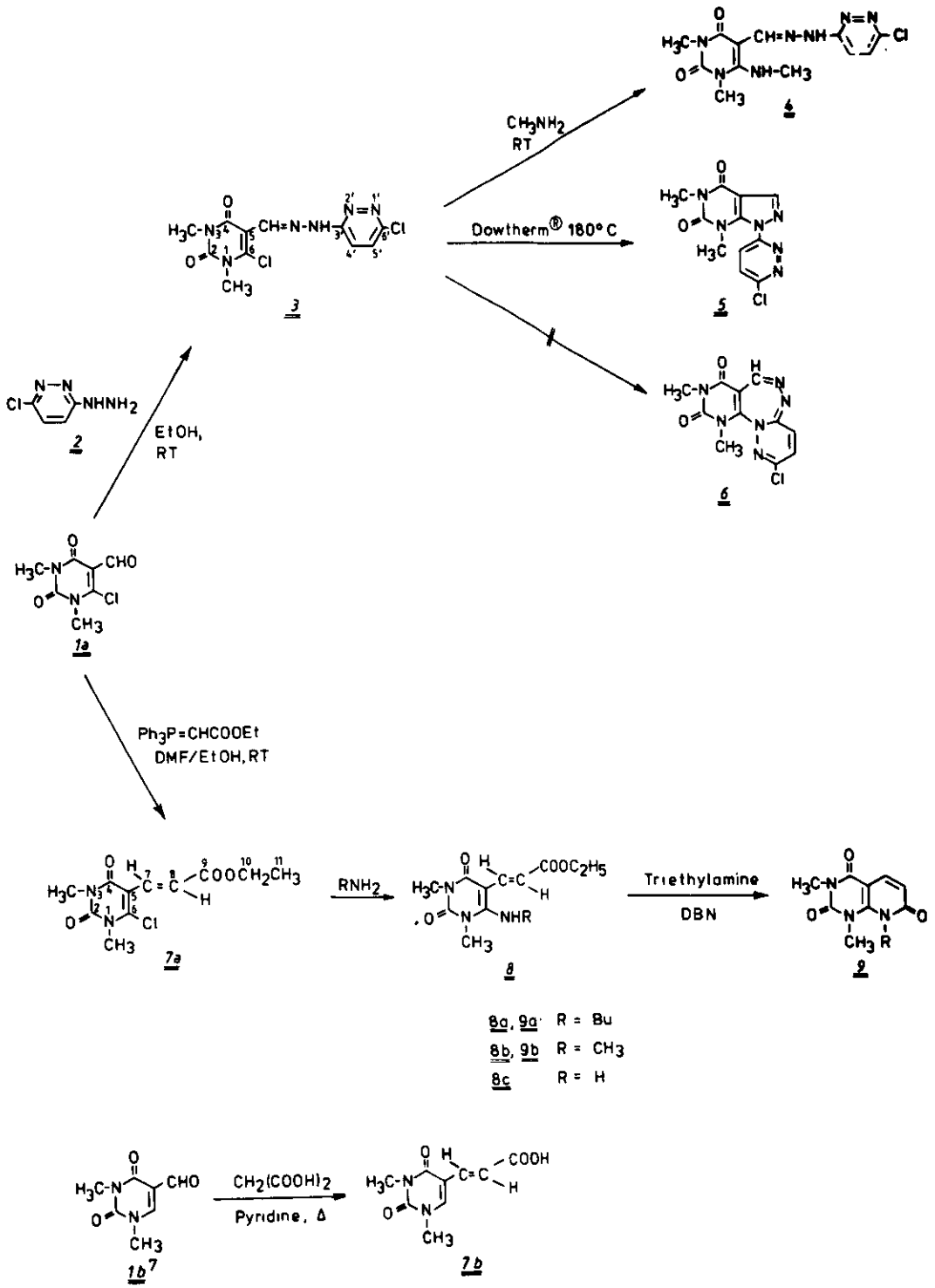

CH3NH2
RT
Dowtherm® 180° C
EtOH,
RT
Ph3P=CHCOOEt
DMF/EtOH, RT
RNH2
Triethylamine
DBN
CH2(COOH)2
Pyridine, Δ
8a, 9a R = Bu
8b, 9b R = CH3
8c R = H

Table 1. List of compounds 3-5, 7a,b, 8a-c, 9a,b, 11, and 12[+]

Comp.	Solvent of Cryst.	M p [°C]	Yield [%]	Molecular Formula
3	ethanol	224-225	90	$C_{11}H_{10}Cl_2N_6O_2$
4	ethanol	313-314	84	$C_{12}H_{14}ClN_7O_2$
5	ethanol	269-270	41	$C_{11}H_9ClN_6O_2$
7a	ethanol	174-175	72	$C_{11}H_{13}ClN_2O_4$
7b	ethanol	281-282	78	$C_9H_{10}N_2O_4$
8a	i-propanol	118-119	54	$C_{15}H_{23}N_3O_4$
8b	i-propanol	170-171	54	$C_{12}H_{17}N_3O_4$
8c	ethanol	237-238	61	$C_{11}H_{15}N_3O_4$
9a	ether	99-100	80	$C_{13}H_{17}N_3O_3$
9b	ethanol	209-210	56	$C_{10}H_{11}N_3O_3$
11	i-propanol	91-92	68	$C_{13}H_{17}N_3O_3$
12	i-propanol	163-164	48	$C_{11}H_{17}N_3O_4$

[+]Satisfactory elemental analyses (C,H,N) and MS data were obtained for all the newly synthesized compounds.

Table 2. IR and ^1H NMR data of compounds 3-5, 7a,b, 8a-c, 9a,b,11, and 12

Comp.	IR (KBr, [cm^{-1}])	^1H NMR ([D_6]DMSO, δ [ppm])
3	1715 (CO), 1670 (CO), 1615 (C=C);	3,22 (s, 3H, 1-N-CH_3), 3.53 (s, 3H, 3-N-CH_3), 7.47 (d, (J=10 Hz), 1H, 4'-CH), 7.63 (d (10), 1H, 5'-CH), 8.16 (s, 1H, CH=N), 11.7 (s, 1H, NH);
4	3205 (NH), 1695 (CO), 1660 (CO), 1615 (C=C);	3.12 (d (6), 3H, NHCH_3)[+], 3.16 (s, 3H, 1-N-CH_3)[+], 3.33 (s, 3H, 3-N-CH_3)[+], 7.24 (d (10), 1H, 4'-CH), 7.56 (d (10), 1H, 5'-CH), 8.42 (s, 1H, CH=N), 9.3 (broad, 1H, NH-CH_3), 11.35 (s, 1H, N-NH);
5	1720 (CO), 1665 (CO), 1615 (C=C);	3.24 (s, 3H, 1-N-CH_3), 3.47 (s, 3H, 3-N-CH_3), 8.18 (d, (9), 1H, 4'-CH), 8.29 (d (9), 1H, 5'-CH), 9.33 (s, 1H, CH=N);
7a	1715 (CO)[+], 1710 (ester CO)[+], 1670 (CO), 1295, 1175 (C-O);	1.22 (t (7.5), 3H, 11-CH), 3.22 (s, 3H, 1-N-CH_3), 3.57 (s, 3H, 3-N-CH_3), 4.17 (q, 2H, 10-CH), 7.10 (d (16), 1H, 8-CH), 7.58 (d (17), 1H, 7-CH);

Table 2. — *Continued*

Comp.	IR(KBr, [cm^{-1}])	^{1}H NMR ([D$_6$]DMSO, δ [ppm]
7b	1730 (CO), 1695 (CO), 1645 (C=C);	3.00 (s, 3H, 1-N-CH$_3$), 3.16 (s, 3H, 3-N-CH$_3$); 6.56 (d, (16), 1H, 8-CH), 7.11 (d (16), 1H, 7-CH), 8.13 (s, 1H, 6-CH);
8a	3345 (NH), 1705 (CO), 1675 (CO);	0.87 (t (6.5), 3H, CH$_3$(Bu)), 1.22 (t (7), 3H, OCH$_2$CH$_3$ (Bu))$^+$, 1.4 (m, 2H, CH$_2$CH$_3$ (Bu))$^+$, 1.7 (m, 2H,NHCH$_2$CH$_2$-), 3.16 (s, 3H, 1-N-CH$_3$), 3.3 (m, 2H, NHCH$_2$)$^\circ$, 3.33 (s, 3H, 3-N-CH$_3$)$^\circ$, 4.11 (q, 2H, OCH$_2$), 6.73 (d (15), 1H, 8-CH), 7.50 (d (15), 1H, 7-CH);
8b	3360 (NH), 1705 (CO);	1.21 (t (7), 3H, CH$_2$CH$_3$), 3.00 (d, 3H, NHCH$_3$), 3.16 (s, 3H, 1-N-CH$_3$), 3.36 (s, 3H, 3-N-CH$_3$), 4.12 (q, 2H, CH$_2$CH$_3$), 6.69 (d (15), 1H, 8-CH), 7.00 (broad, 1H, NH), 7.62 (d (15), 1H, 7-CH);
8c	3380, 3250 (NH), 1690 (CO), 1670 (CO);	1.22 (t (7), 3H, CH$_2$CH$_3$), 3.14 (s, 3H, 1-N-CH$_3$), 3.36 (s, 3H, 3-N-CH$_3$), 4.13 (q, 2H, CH$_2$CH$_3$), 6.96 (d (15), 1H, 8-CH), 7.67 (d (15), 1H, 7-CH);
9a	1715 (CO), 1665 (CO);	0.84 (t (7), 3H, CH$_2$CH$_3$), 1.32 (sx, 2H, CH$_2$CH$_3$), 1.68 (qui, 2H, NCH$_2$CH$_2$-), 3.22 (s, 3H, 1-N-CH$_3$), 3.50 (s, 3H, 3-N-CH$_3$), 4.16 (t (7.5), 2H, N-CH$_2$-), 6.29 (d (9), 1H, 6-CH), 7.85 (d (9), 1H, 5-CH);
9b^{++}	1715 (CO), 1660 (CO);	3.38 (s, 3H, 3-N-CH$_3$), 3.57 (s, 3H, 1-N-CH$_3$), 3.59 (s, 3H, 8-N-CH$_3$), 6.37 (d (9), 1H, 6-CH), 7.95 (d (9), 1H, 5-CH);
11^{++}	1710 (CO), 1665 (CO);	0.98 (t (7), 3H, CH$_2$CH$_3$), 1.44 (m, 2H, CH$_2$CH$_3$), 1.80 (m, 2H, O-CH$_2$CH$_2$-), 3.46 (s, 3H, 1-N-CH$_3$), 3.67 (s, 3H, 3-N-CH$_3$), 4.44 (t, 2H, -O-CH$_2$-), 6.58 (d (9), 1H, 6-CH), 8.29 (d (9), 1H, 5-CH);
12^{++}	3340, 3360 (NH), 1705 (CO), 1680 (CO);	1.24 (t (7), 3H, 11-CH), 2.63 (s, 4H, 7,8-CH), 3.32 (s, 3H, 1-N-CH$_3$), 3.44 (s, 3H, 3-N-CH$_3$), 4.10 (q, 2H, 10-CH), 5.32 (s, 2H, NH$_2$);

$^{+,\circ}$ superimposed signals

$^{++}$ ^{1}H NMR spectrum in CDCl$_3$ solution.

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